

Chemoradiotherapy in Esophageal Cancer

Toxicity is in the Eye of the Beholder

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Dr. Murthy and colleagues report, in this issue of the *Journal of Thoracic Oncology*, potential long-term complications in patients undergoing preoperative chemoradiotherapy for esophageal cancer.¹ They compared patients treated with preoperative chemoradiotherapy to a group of patients undergoing esophagectomy alone at the Cleveland Clinic. They report that the use of preoperative chemoradiotherapy led to an increased rate of late pleural and pericardial effusions. Despite this observation, there was no significant increase in the need for intervention to treat these complications, and there was no adverse impact on patient survival.

The use of preoperative chemoradiotherapy in esophageal cancer has evolved as a therapy standard at most cancer centers in the United States. Although there are not clear cut phase III data to indicate a survival benefit for this approach compared with surgery alone, individual trials generally have been small and underpowered. Nearly all trials indicate trends toward improved survival with the use of preoperative chemoradiotherapy, in particular in patients achieving a pathologic complete response. Meta-analyses also support a survival benefit for preoperative chemoradiotherapy.² A recent phase III trial from Germany indicated strong trends for superior survival and local tumor control for the use of combined preoperative chemoradiotherapy compared with preoperative chemotherapy alone, in high risk patients staged T3 or T4 with endoscopic ultrasound and laparoscopy.³ Although collectively the published literature indicates a survival benefit for combined preoperative chemoradiotherapy, the absolute survival improvements ranging from 10 to 20% are modest at best. As the authors indicate in their current series, this potential modest improvement in survival may come at the cost of an increase in potential late complications.

Is toxicity of all chemoradiotherapy comparable? Most series report only short-term perioperative complications after combined chemoradiotherapy and indicate the approach is safe and tolerable. However, toxicity is also likely to vary by the chemotherapy regimen, dose, and schedule, as well as the dose and fractionation schedule of radiotherapy. The authors in the current series either used intermittent, high dose infusional fluorouracil (5-FU) with high dose cisplatin, or the use of a high dose, every 3 week schedule of cisplatin and paclitaxel. This chemotherapy was combined with a twice daily hyperfractionated schedule of radiotherapy. Both of these approaches are likely to increase short-term toxicities of chemoradiotherapy. Hyperfractionated radiotherapy consistently results in more acute radiation related toxicities than once daily fractionation in many studies,⁴⁻⁶ and such a dose and schedule of radiotherapy has neither been compared with, nor shown to be superior to, once daily fractionation. In addition, chemotherapy schedules employing lower dose, weekly administration of chemotherapy, as opposed to high dose chemotherapy administered weeks 1 and weeks 3 to 5, also tend to lessen acute toxicities of chemoradiotherapy.^{7,8} Phase II trials employing weekly chemotherapy without 5-FU have reported potentially lower rates of esophagitis, lesser need for the placement of feeding tubes, and often less hematologic toxicity. Whether or not alternative chemotherapy or radiotherapy schedules would impact on the development of late onset toxicities, such as pleural and pericardial effusions, is unclear. Cooperative groups including Eastern

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Cooperative Oncology Group and Cancer and Leukemia Group B are exploring weekly chemotherapy regimens without traditional infusional 5-FU, based on phase II trials indicating favorable rates of GI and hematologic toxicities with these alternative regimens.

Chemoradiotherapy as a preoperative approach in esophageal cancer is likely here to stay. Progress, however, clearly needs to be made with the evaluation of novel systemic agents, including targeted therapies, given the limited benefit of currently available therapy. Drugs targeting the epidermal growth factor receptor, including Cetuximab, and the vascular endothelial growth factor receptor, including Bevacizumab, are now in active phase II and III clinical trials in combined modality therapy in esophageal cancer.

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